44. A method of treating diabetes or obesity in a mammal in need thereof comprising administering the composition of Claim 40 to the mammal.

45. A method of treating diabetes or obesity in a mammal in need thereof comprising administering the composition of Claim 42 to the mammal.

46. A composition comprising individual flat rod shaped or plate-like crystals of Val-8-GLP(7-37)OH, wherein said crystals remain suspended in liquid medium for a longer period of time than crystalline clusters or amorphous crystals.

REMARKS

Interview Summary

On February 23, 2000, a telephonic interview was held between Steven G. Davis, Attorney for Applicants, and Examiner F. Moezie. The Examiner is thanked for granting the interview and for her helpful comments during the interview.

During the interview, the prior art rejections and rejection under 35 USC 112, first paragraph were discussed. It was agreed that Applicants would submit evidence in the form of a Declaration that showed that the claimed glucagon-like peptide 1 (GLP) crystals differed from the prior art.

Applicants' Attorney wishes to clarify a statement in the Examiner's Interview Summary. This statement says that the GLP crystals would have to be claimed by the process of making them. Although product by process claims were discussed during the interview, Applicants' Attorney understood from the discussion that product by process claims were one option for claiming the GLP crystals, but

not the only option. In fact, claim language referring to "a composition comprising crystals having [a particular morphology]" was discussed. Moreover, it was agreed that claim language of this type might be acceptable.

Claim Amendments

Claims 1-25 have been cancelled and replaced with new Claims 26-46.

Support for Claims 26 and 33 is found on page 4, lines 15-20 and page 11, lines 13-26.

Support for Claims 27-28 and 34-35 is found on page 11, lines 13-26.

Support for Claims 29 and 36 is found on page 11, lines 27-29.

Support for Claims 30-31 and 37-38 is found on page 12, lines 10-17.

Support for Claims 32 and 39 is found on page 12, lines 3-9.

Support for 40-41 is found on page 10, lines 1-8 and page 13, lines 15-17.

Support for Claim 46 is found on page 4, lines 1-6.

Rejection of Claims 7-22 Under 35 USC 112, First Paragraph

A. New Claims 26-46 are enabled by the specification

Claims 7-22 were rejected as allegedly containing subject matter not enabled by specification. Specifically, the Examiner stated that due to the wide range of structural diversity among the GLP compounds claimed, "Each category of compounds mentioned above would have to be tried for crystal formation on its own merits".

Applicants respectfully disagree with the rejection. However, to expedite prosecution, Claims 1-25 have been cancelled and replaced with new Claims 26-46. These new

claims are directed to a composition comprising crystals of valine-8-GLP-1(7-37)OH having a particular morphology, (Claims 40 - 42 and 46), processes for preparing said composition (Claims 26 - 33) and crystals valine-8-GLP-1 (7-37)OH prepared by said process (Claims 34-39). The process for preparing these crystals of valine-8-GLP-1(7-37)OH is exemplified in Examples 1-8 and 10-18. Therefore, new Claims 26-46 are fully enabled by the specification of the subject application. Withdrawal of the rejection is requested.

B. Multiple morphologies are formed by the claimed method

During the telephonic interview on February 23, 2000, the Examiner expressed doubt that multiple crystal forms (polymorphs) could be produced. The disclosed method, in fact, produces individual rod-shaped and plate-like crystals. To support Applicants' assertion that both crystal morphologies form, "The Growth and Preliminary Investigation of Protein and Nucleic Acid Crystals for X-Ray Diffraction Analysis" by Alexander McPherson in Burtis, *et al.*, METHODS OF BIOCHEMICAL ANALYSIS, Volume 23, pages 249-345, is enclosed herewith as Exhibit A. The last full sentence on page 253 and the legend to Figure 1 read as follows:

> A striking illustration of the multiminima behavior is seen in the extensive polymorphism of crystal forms exhibited by many proteins and nucleic acids.
>
> Polymorphism in transfer RNA crystals is the simultaneous presence of hexagonal and cubic forms in the same sample of mother liquor.

Thus, it is seen that polymorphism among protein crystals such as V8-GLP is not only possible, but common.

Rejection of Claims 7-22 Under 35 USC 112, Second Paragraph

The Examiner stated that the use of "or" following the phrase "from the group consisting of" in Claims 7-9, 12 and 14 is improper. These claims have been cancelled. The objection is now moot. Withdrawal is requested.

Rejection of Claims 7-22 Under 35 USC 102(b) or in the alternative, under 35 USC 103(a) in view of EP 619,322 or Kim *et al., Pharmaceutical Research 12:*1644 (1995)

The Examiner stated that EP 619322 and Kim, *et al.* teach that crystalline forms of GLP-1 are known in the art. Therefore, the Examiner concluded that the subject matter of Claims 7-22 are anticipated or rendered obvious in view of these references. Applicants respond to the rejection in the sections below:

A. Applicants' Invention

Claims 1-25 have been cancelled and replaced with new Claims 26-46. These claims refer to a single compound, valine-8-GLP-1(7-37)OH, as opposed to the cancelled claims, which referred to GLP compounds in general.

Claims 40-42 and 46 are directed to a new crystal form of Valine-8 GLP-1 (7-37)OH. This new crystal form is required to have a particular morphology, specifically flat rod shaped or plate-like morphology. The claimed compositions are also required to comprise individual crystals, as opposed to clusters. These new Valine-8 GLP-1 (7-37)OH crystals (hereinafter referred to as "V8-GLP crystals") have a number of advantages over GLP crystals of the prior art, which are clusters of needles, microcrystals or amorphous solids. Specifically, when suspended in solution, Applicants' claimed crystals sediment more slowly than the GLP crystals in the prior art. Thus, they are more

suitable for use in pharmaceutical formulations for injection.

The superior sedimentation property of Applicants' new crystals is consistent with the presence of about 2-15% (v/v) ethanol or 2-15% (v/v) propanol or a mono or disaccharide in the crystallization solution. Claims 26-32 are directed to a method of producing V8-GLP crystals by crystallizing from a solution comprising these constituents; and Claims 33-39 are directed to V8-GLP crystals produced by said process.

B. Crystals of Valine-8 GLP-1 (7-37)OH are not disclosed by Kim *et al.* or the EP 619,322 and are therefore novel

Claims 40-42 and 46 are directed to novel crystal forms of V8 GLP-1 (7-37)OH. In contrast, Kim *et al.* and the EP 619,322 only disclose the crystallization of GLP-1 (7-36)NH_2 and insulinotropin, which is another name for GLP-1 (7-37)OH (see first full paragraph on page 1665 of Kim *et al.* and the examples in EP 619322). In fact, Kim *et al.* and EP 619322 do not even mention V8 GLP-1, which differs from GLP-1 (7-37)OH and GLP-1 (7-36)NH_2 at the eight position (valine substitutes for alanine). Therefore, the subject matter of Claims 40-42 and 46 is novel in view of Kim *et al.* and EP 619322.

Claims 26-32 are directed to methods of producing V8-GLP from a crystallization solution comprising 2-15% (v/v) ethanol or 2-15% (v/v) propanol or a mono or disaccharide; Claims 33-39 are directed to V8-GLP crystals produced by said process. In contrast, none of the crystallization procedures disclosed in Kim *et al.* and EP 619322 use a crystallization solution comprising 2-15% (v/v) ethanol, 2-15% (v/v) propanol or a mono or disaccharide. Therefore,

Claims 26-32 and 33-39 are novel in view of Kim, *et al.* and EP 619322.

C. The morphology of the claimed crystal compositions differ from the morphology of the GLP crystals in the prior art

The claimed composition is required to contain ***individual*** flat rod shaped or plate-like crystals of V8-GLP. In contrast, the morphology of GLP crystals formed by methods disclosed in the prior art is either ***clusters*** of needles or microcrystals. Support for this assertion is provided in the Declaration under 37 CRF 1.132 by Chakravarthy Narasimhan, Ph.D. (hereinafter, the "Narasimhan Declaration"), which is enclosed herewith and is discussed in the subsections below:

1. The GLP crystals formed in Kim, *et al.* are clusters of needles.

The first full paragraph on page 1665 of Kim *et al.* states that "needle or blade-like crystals [of GLP-1 (7-37)OH] started forming within 5 to 6 hours". The GLP-1 (7-37)OH crystals obtained in Kim *et al.* are shown in Figures 1A-1C and are plainly a mixture of individual needle-like crystals and clusters of needles. When V8-GLP was crystallized by the method disclosed in Kim *et al.*, clusters of plate-like crystals were obtained (see Section 7c of the Narasimhan Declaration). In contrast, the compositions claimed by Applicants comprise individual flat rod-shaped or plate-like crystals of V8-GLP. Because the morphology of the crystals in Applicants' claimed composition differ from the morphology of the crystals disclosed in Kim, *et al.*, the claimed crystalline composition are novel in view of Kim, *et al.*

2. The morphology of the GLP crystals disclosed in EP 619322 differs from Applicants' crystals

EP 619322 discloses GLP crystals which includes the following morphologies: microcrystals - Examples 35-36; and needle shaped clusters - Example 44. In contrast, the compositions claimed by Applicants comprise individual rod-shaped or plate-like crystals of V8-GLP.

The morphology of Applicants' V8 GLP crystals is consistent with the presence of ethanol, propanol, a monosaccharide or disaccharide in the crystallization solution (Section 9 of the Narasimhan Declaration). Support for this assertion is provided by Sections 5-8 of the Narasimhan Declaration, which describe an experiment in which clusters were obtained from V8 GLP crystallizations from aqueous solutions containing no ethanol. Specifically, Example 45 of EP 619322 and the crystallization procedure disclosed in Kim *et al.* were repeated with V8 GLP. In both cases, clusters were obtained. Further support is provided in Examples 2-4, 5-7, 9-10, and 12-17 of the subject specification, in which individual crystals were obtained when ethanol, a monosaccharide or disaccharide was present in the crystallization solvent. Significantly, the amount of individual crystals relative to the amount of clusters increases as the amount of ethanol in the crystallization solvent (see Examples 1-4, 5-7).

EP 619322 discloses a number of other crystallizations from water without describing the morphology of the resulting crystals. Consistent with the evidence discussed in the previous paragraph, it appears that these procedures result in crystalline clusters, without the presence of individual crystals. This is consistent with the evidence discussed in the previous paragraph.

In summation, the claimed crystalline compositions are novel in view of EP 619322 because, *inter alia*, the morphology of crystals in these composition differs from the morphology of the crystals disclosed in EP 619322.

D. Applicants' crystalline compositions have superior sedimentation properties compared with the crystalline compositions disclosed in EP 619322 and Kim *et al.* and are therefore non-obvious

The V8 GLP crystals in Applicants' claimed compositions have superior sedimentation properties compared with the GLP crystals disclosed in the prior art and formed from crystallization procedures disclosed in the prior art. Support for this assertion is provided in the Narasimhan Declaration, which is discussed in the following paragraphs.

To provide extended time actions, GLP compounds can be formulated as a crystal suspension and injected subcutaneously. Crystal suspensions of GLP compounds are discussed in Sections 3 and 4 of the Narasimhan Declaration. To administer the GLP compound subcutaneously as a crystal suspension, GLP crystals are suspended in an aqueous medium. After gently shaking the crystal suspension, a suitable dose is drawn into a syringe and injected. To ensure that uniform and correct doses are reproducibly administered, it is critical that the GLP crystals remain uniformly suspended throughout the solution while the dose is being drawn into the syringe. Therefore, GLP crystals which sediment slowly are clearly superior to GLP crystals which sediment quickly.

Sections 4-7 of the Narasimhan Declaration describe experiments which show that the V8-GLP crystals disclosed in the subject application sediment more slowly than V8-GLP crystals produced by methods disclosed in the prior art. Specifically, Section 7 reports the sedimentation rate of Applicants' V8 GLP crystals and the sedimentation rate of V8

GLP crystals produced by three different prior methods. Crystals remain suspended longer as the sedimentation rate decreases. As can be seen from the Table in Section 7, Applicants V8 GLP crystals have the lowest sedimentation rate and are therefore superior to those produced by prior art methods when administered subcutaneously as a crystal suspension. For this reason, Applicants' V8 GLP crystalline compositions are non-obvious over EP 619322 and Kim *et al.*

Applicants' V8 GLP crystal composition comprises individual flat rod shaped or plate-like crystals, regardless of whether they are formed by crystallization from an aqueous solution containing 2-15% ethanol (v/v) or 2-15% propanol (v/v) or a mono or disaccharide (see Examples 9-10 of the subject application). The superior sedimentation properties of crystal compositions crystallized from aqueous/ethanol solutions were demonstrated in the experiments described Section 5-8 of the Narasimhan Declaration. Other compositions with crystals of the same morphology, including Applicants' V8 GLP crystals formed from aqueous/propanol and mono or disaccharide-containing solutions, should also have these superior sedimentation properties. Therefore, V8-GLP crystals formed from an aqueous crystallization solution containing 2-15% propanol (v/v) or a monosaccharide or disaccharide are also non-obvious over the prior art.

Rejection of Claims 7-22 under 35 USC 103(a) in view of EP 619,322 or EP 658,468 further in view of US Patent No. 5,734,026

The Examiner stated that each EP reference teaches that crystalline GLP compounds are known in the art. For example, page 7, lines 2-10 of EP 658,468 states that "a crystalline or amorphous suspension is isolated and purified using

standard techniques". The Examiner stated further that the primary references do not teach purification techniques but that these are taught in US Patent No. 5,734,026.

Prior Art Cited in the Rejection

The teachings of EP 619,322 are summarized in the prior section of this Amendment.

EP 658,468 teaches crystallizing GLP molecules from solutions that are completely aqueous (page 6, line 46 through page 7, line 5 and Example 2). Crystallization from solutions containing ethanol, propanol or a saccharide is not taught or suggested.

US Patent No. 5,734,026 teaches crystallization methods for human growth hormone (see Summary of the Invention). Crystallization techniques for GLP compounds are not taught or suggested.

Applicants' Crystallization Procedure Provides V8 GLP Crystals Having Superior Sedimentation Properties Compared With V8 GLP Crystals Obtained by Methods Disclosed in the Prior Art

Applicants respectfully submit that U.S. Patent No. 5,734,026 (the "'026 Patent") is completely irrelevant to the patentability of the claimed invention. This reference teaches methods for crystallizing human growth hormone, which is a protein having 191 amino acids (column 1, lines 12-15 of the '026 Patent). In contrast, GLP compounds have about 31 amino acids. GLP compounds and human growth hormone are so different that any crystallization technique applicable to one is not relevant to crystallizing the other, unless there is specific evidence to the contrary.

Even if the '026 Patent were relevant to the patentability of the claimed invention, the subject matter

of Claims 26-46 is still non-obvious over the cited prior art. Support for this position is provided in the following paragraphs.

As discussed in the previous section of this Amendment, Applicants' crystallization method produces crystals of V8 GLP with superior sedimentation properties and different morphologies. These superior sedimentation properties and morphologies appear to be due to the presence of specific amounts of ethanol or propanol or a mono or disaccharide in the crystallization solution. Crystallizations from aqueous solutions without these additives appear to produce crystals with poorer sedimentation properties and different morphologies. Support for these assertions is provided by results present in the Narasimhan Declaration, which is also discussed in detail in the prior section of this Amendment.

As noted above, EP 658,568 discloses crystallization procedures which use solvents without alcohols or saccharides. Therefore, V8 GLP crystals produced by these procedures have inferior sedimentation properties. V8 GLP crystals produced by methods disclosed in EP 619,322 have already been shown in the previous section of this Amendment to have inferior sedimentation properties.

US Patent No. 5,734,026 (the "'026 Patent") does not cure the deficiencies of EP 619,322 and EP 658,568 because it does not suggest any modification in crystallization procedures which would provide V8-GLP crystals with improved sedimentation properties.

In summation, V8 GLP crystals produced by Applicants' methods have superior and unexpected sedimentation properties compared with the GLP crystals produced by methods disclosed in EP 619,322 and EP 658,568. Because none of the cited references, including the '026 Patent suggest any modification in these methods that would result in V8

GLP crystals having these superior sedimentation properties, Applicants' claimed compositions comprising V8 GLP crystals are non-obvious in view of the references cited in the Office Action.

Rejection of Claims 7-22 in View of US Patent No. 5,977,071 Under the Judicially Created Doctrine of Obviousness Type Double Patenting

US Patent No. 5,977,071 (the "'071 Patent") claims and discloses crystalline GLP compounds. However, the '071 Patent only discloses crystallization of GLP compounds from water (see column 10, lines 8-28 and Example 2). The addition of ethanol, propanol or a saccharide is neither claimed, taught nor suggested.

As discussed in the previous sections of this Amendment, Applicants' crystallization method produces crystals of V8 GLP with superior sedimentation properties and different morphologies. These superior sedimentation properties and morphologies are due to the presence of specific amounts of ethanol or propanol or a mono or disaccharide in the crystallization solution. Crystallizations from aqueous solutions without these alcohols or saccharides produce crystals with poorer sedimentation properties and different morphologies. Support for these assertions is provided by results present in the Narasimhan Declaration, which is also discussed in detail in the prior sections of this Amendment.

As noted above, EP 658,568 discloses crystallization procedures which use water as a crystallization solvent without alcohols or saccharides. Therefore, V8 GLP crystals produced by these procedures have inferior sedimentation properties. Because there is no teaching or suggestion in the '071 Patent, either in the claims or specification, of

how to modify these crystallization methods so as to obtain V8 GLP crystals with these superior sedimentation properties, Applicant's claimed compositions and methods are non-obvious in view of the claims and teachings of the '071 Patent.

SUMMARY AND CONCLUSION

In view of the remarks and amendments provided herein above, it is respectfully submitted that the rejections have been overcome. Reconsideration and withdrawal of the rejection are therefore requested.

If the Examiner feels that a telephone conversation with Applicants' Attorney would be helpful in expediting the prosecution of this case, the Examiner is urged to call Applicants' Attorney at (317) 276-0280.

Respectfully submitted,

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